Members of WCC-60, a Coordinating Committee on Science and Management of Pesticide Resistance, support permitting specific exemptions for resistance management. Growers and pesticide registrants should be better able to manage resistance and reduce losses with rapid access to new pesticides through Section 18 registrations.

The primary goal of resistance management is to prevent or delay the development of pesticide resistance in target pests. Thus management strategies need to be implemented when a chemical is registered. Given this premise, it should be justifiable to request a specific exemption based on prior development of resistance elsewhere in the world or on the likelihood of resistance development in the United States.

Secondarily we try to manage pests after resistance is known to exist, at least at low frequencies. Successfully managing pests after resistance is recognized requires a rapid response to (1) limit the increase in frequency of resistant strains and (2) successfully control the target pest despite failures of the key pesticide that is the victim of resistance. Additionally, we should be striving to avoid crop losses, which also mean responding early in resistance development. Thus crop loss due to resistance should not be considered required documentation for supporting a specific exemption request.

Pesticides at risk for resistance typically provide better control than protectant (contact) chemicals because the at-risk chemicals usually are systemic. Systemic fungicides, herbicides, and insecticides can move within a plant providing better control. Systemics are active at places like the underside of leaves where conditions are more favorable for many insects and pathogens. Thus protectants already registered for a pest cannot replace systemics when resistance develops. Although not suitable as a replacement, protectants often play an important role in resistance management because they control resistant strains as well as sensitive ones, and they do not contribute to the problem as they usually have low resistance risk. This important role must be remembered when re-registration decisions are made.

In some situations it may be desirable to allow a waiver of item iii in the list of 4 criteria for emergency exemption requests. Permitting requests for more than one chemical would be warranted when, at the time of the request for a specific exemption, the following conditions were met: 1) the chemical now affected by resistance was previously the only one registered that was not affected by resistance, 2) strains resistant to this chemical are already widespread and at a high frequency in the pest population thereby rendering a reduced efficacy, and 3) potential replacement chemicals have high risk for resistance development. For example, Section 18 requests were made in 1998 for both Nova and Quadris for powdery mildew of cucurbits. The request was made after resistance to Bayleton (triadimefon) had reached a point that this fungicide was no longer effective and the other systemic fungicide registered, Benlate (benomyl), had been plagued by resistance for years. It was too late in resistance development to manage resistance development through registration of just one chemical. Bayleton and Benlate both needed to be replaced. Obtaining registration of both Nova (myclobutanil) and Quadris (azoxystrobin) allowed growers to manage resistance to both of these fungicides through an alternation program. Thus this is a good example of a situation where an emergency exemption request for two chemicals was justifiable. On the other hand, perhaps development of resistance to Bayleton could have been slowed if it had been possible to request a Section 18 for resistance management when resistance first started to occur in the late 1980s and a suitable chemical was available. At that time Nova was registered for use on other food crops.

The following comments are in regard address the requests under item 4 on page 20155 for comment on specific points.

i. What level of documentation would be appropriate through laboratory, greenhouse, or field studies either in county, state, region, inside or outside the U.S.?

If this provision is going to be useful, the information requested must be deliverable in a reasonable format and in a reasonable time frame. Flexibility will be needed. Ideally, pest managers and resistance researchers need someone with experience assessing pesticide sensitivity in the target pest and funds to cover the cost of conducting the tests. Ideally sensitive or susceptible strains are needed for comparison, but these are costly to maintain. Documentation of both susceptibility and resistance will vary with the pest. Some pests will have excellent baseline data and even a discriminating dosage assay system in place. In other instances, say for example a recently introduced insect pest, very little information may be available other than failure of a product or products in the field in numerous locations. How will the Agency develop a sensitive data requirement system that provides alternatives to the field in a timely manner? We suggest that the Agency consider a sliding scale data request. Perhaps three levels of data based on the pest's resistance history, the availability of base line data and the availability of field-based resistance assay tools. Essentially, we are advocating that EPA make determinations on a 'case-by-case, weight-of-the-evidence basis' and also common sense basis. If there is a hard and fast rule the Agency will not be able to provide an adequate response when a new and very different event occurs to allow the affected industry to react appropriately. One suggestion is to use the Arthropod Resistant Database (http://whalonlab.msu.edu/rpmnews/) which includes and array of information including monitoring information, base-line information and resistance levels by pest and compound.

ii. How should noted resistance in related pest species be used to aid a request?

Resistance developing in a related pest species or resistance developing in the target pest under laboratory conditions is valuable information and should be used when available to justify a Section 18 request, but this information should not be required or considered conclusive of what will happen to in the target pest in nature. However, in the absence of specific data for a species, a closely related species could give limited insight as to the capacity for resistance in the target species.

iii. How many years of field data and how many geographic locations would one need to establish a reasonable case for pest resistance?

The answer depends partly on the pest and previous experience with resistance elsewhere. One year in one location could be enough with a pest known to be capable of long-distance dispersal and/or known to have developed resistance to the chemical outside the USA. If the goal is to manage resistance we need to respond promptly. It would be unwise to wait until resistance is well established and widely known.

Just as resistance changes over time, our definition of resistance has been developed and refined. A panel of experts of the World Health Organization defined resistance as follows: "Resistance to insecticides is the development of an ability in a strain of insects to tolerate doses of toxicants which would prove lethal to the majority of individuals in a normal population of the same species". (WHO, 1968). Although this definition was a very good start, it is not the complete story as we now know. After more than 60 years of use of synthetic insecticides, pest populations have been selected all over the world to one or more pesticides so that is very hard to find a "normal population, " where "normal" means a susceptible field population, never having been exposed to pesticides. In addition, the definition considers populations and not individuals, a condition that is more important today because new biochemical and physiological techniques facilitate the detection of resistance in single individuals. Moreover, screening of very low frequency of resistance alleles, especially important for plant pesticides such as Bt toxin producing crops, would not fit the WHO definition.

A more inclusive definition that considers single individuals as well as populations is provided by Crow (1960): "resistance marks a genetic change in response to selection." This definition is not restricted to high resistance levels. Incipient resistance also is included in this term (Sawicki 1987). However, it is missing the significance of "field-failure" of a pesticide due to resistance. Sawicki (1987) improved this definition by adding the significance of field-failure as follows: "Resistance marks a genetic change in response to selection by toxicants that may impair control in the field." In this definition is left opened the possibility that resistance may (or may not) impair control in the field.

The near exponential increase in the world-wide cases of resistance, combined with scientific and public pressure, led the pesticide industry to form various "resistance action committees" (Insecticides = IRAC, Fungicides= FRAC, Herbicides = HRAC) to work in different aspects of the management of resistance, and specifically monitoring programs. The criteria developed by the industry (e.g. IRAC) for defining resistance are:

1) The product has to be labeled for the pest and have a history of performing successfully;
2) product failure isn't a consequence of incorrect handling, storage or application;
3) the recommended dosage fails to suppress the pest population below an economic threshold; and
4) failure to control is due to a genetic change in susceptibility passed down to successive generations.

Although the IRAC criteria are sufficient to ensure that a pest has truly developed resistance, the definition is still problematic for early detection of resistance. For example, a recommended dose cannot fail to suppress a pest population below an economic threshold. However, if the frequency of resistant individuals are present, but not in enough numbers to cause field failure, resistance would not be detected. A possible result of this situation is an increase in the frequency of resistant individuals in the next generation. On the other hand, a correct insecticide application could guarantee reduction of pest populations below an economic threshold, other factors rather than application may affect reduction. These factors could be predators presence, pest spatial distribution, crop phenology, stage of the pest, and frequency of resistant individuals (Roush, 1991). Therefore, special care has to be taken in the interpretation of this definition. By the time that field applications fail to control a pest population, it most probably is too late to implement strategies for the management of resistance to this pesticide, and other pesticides if the insect is cross-resistant to (due to the high frequency of resistant individuals). Clearly early detection of resistance is an important aspect missing in this definition.

iv. Comments are requested on the documentation of cross-resistance potential.

It is valuable to have information on cross-resistance potential, but it is not possible to examine this until resistance has developed. If the information is available, it should be considered, but it shouldn't be a requirement for an emergency exemption. In many situations we will be relying on information from other areas of the world where the chemical has been registered longer and resistance has already developed. When there is more than one candidate chemical for an emergency exemption and there is no information on cross-resistance potential, it would be prudent to grant exemptions to both chemicals. This would provide more tools for the resistance management program.

v. Should emergency exemptions for resistance management be limited to requests for chemicals in a different class, or with a different mode of action, than the chemical to which resistance is developing?

When resistance is quantitative, it can be possible to regain control and manage resistance by replacing the pesticide affected by resistance with a more active chemical in the same class and/or with the same mode of action. For example, resistance to DMIs (fungicide group 3) in the cucurbit powdery mildew fungus does not appear to have continued developing since 1998 when the DMI Nova became available for commercial use to replace the first DMI registered, Bayleton, which had become ineffective due to resistance. Nova continues to provide good control when used at a high labeled rate. Limited testing of isolates has not revealed a shift in sensitivity since 1998.

Cross resistance is not an absolute between chemicals in the same class or with the same mode of action. . In some instances, for example codling moth resistance to organophosphates, negative cross resistance occurred between azinphosmethyl and chlorpyriphos such that resistance to one potentiated mortality when the other was sprayed. Similar negative cross resistance episodes occurred with resistant green peach aphids selected in potato fields with organophosphates, carbamates and synthetic pyrethroids targeting Colorado potato beetles were much more susceptible to methamidophos used later in the season to arrest aphid vectoring of leafroll virus.

vi. What evidence should be provided to demonstrate the likely effectiveness of proposed management strategies to manage resistance?

Resistance Management Strategies are essentially anti-evolution strategies. Resistance managers are attempting to reduce the inheritance of resistance genes in the next generation(s) of a target pest. To accomplish this, essentially a range of Agency incentives, scientific principles and practical strategies, tactics and tools must be considered (in outline format following);

- Pest Life History
  - Reproductive rate of pest
  - Number of generations per year
  - Seed dormancy / seedbank longevity
  - Outcrossing versus self-pollination
  - Mobility of pest population
    - gene flow among selected and unselected populations
  - Host range of pest
    - polyphagous species tend to have more untreated habitats (refuges from selection)
- Agroecosystem Structure
  - crop diversity and placement
- IPM & Crop Production Practices
  - crop rotations & production seasons
  - pest diversity
  - role of non-chemical controls
- Pesticide Use Practices
- Pesticide attributes
  - short residual activity
    - minimizes low dose selection

    - mode of action & cross resistance
- Method of application
    - uneven coverage may kill SS but allow RS to escape
- Timing applications
    - scouting and thresholds
    - targeting particular stages
- Refugia from selection preserve SS homozygotes (for sexually reproducing pests)
    - SS by RR mating produces RS offspring
    - if resistance is functionally recessive, RS individuals may be killed
- Spatial Refugia (for sexually reproducing pests)
    - habitat in which selection does not occur
        - spot treatments
        - untreated habitat (crop or non-crop)
- Temporal Refugia (for sexually reproducing pests)
    - periods of time during which selection does not occur
        - short residual toxicants
        - timed applications

Goals of Resistance Management should be:

- Preserve susceptibility
- Prolong useful life of specific control measures
- Avoid need for more costly management measures
- Prevent control failures
- Prevent economic loss
- Stabilize IPM

Principles of Resistance Management include:

- Begin when frequency of R alleles is low
    - Before resistance is a problem
- Involve growers, extension personnel, crop consultants, ag-chem. Industry, dealers
- Minimize differential mortality of resistant and susceptible genotypes
    - multiple, alternative management tactics
    - use thresholds
    - short residual activity compounds
    - target specific life stages
    - thorough coverage
    - provide refugia (for sexually reproducing pests)
- Pesticide choice
    - compatible with IPM program
    - no cross resistance
    - short residual activity
    - diversify modes of action
    - narrow spectrum
- Pesticide use strategies
    - Mixtures
        - kill genotypes resistant to one pesticide
    - Alternations across generations

        - restrict exposure
        - decline of R allele frequency due to
            - fitness costs
            - immigration of SS
- High dose (kill RS and intermediately resistant strains)
    - difficult to maintain with conventional pesticides
    - feasible with transgenic plants
        - high + refuge is major strategy for transgenic crops

Elements of Resistance Management include:

- Define specific objectives
- Formulate best-guess strategy
- Education
- Implement
- Monitoring
- Modify

Attributes of Resistance Management Programs include:

- Simple
- Robust
- Compatible with
    - production system
    - business requirements and plans
    - regulatory environment
    - information systems

If the agency would increase Resistance Management Programs it would be wise to:

- Increased incentives
    - Increasing costs of discovery, development, registration
    - Interest of EPA
- Increased opportunities
    - Consolidation in Ag. Chem industry
    - New classes of active ingredients
- Expanding knowledge and experience

We do not have much evidence on efficacy of resistance management strategies except in an anecdotal manner. We cannot evaluate strategies for a particular chemistry until resistance has developed; once evaluation is completed it likely will be too late to use the information or there are too little human and capital resources to target the situation and get necessary information in a timely manner. Therefore, at this time it is not practical to require any evidence demonstrating the likely effectiveness of proposed resistance management strategies, rather take a scientific approach by essentially expecting that the petitioner adhere to a set of the above principles, strategies, tactics and tools. In all cases, proposed strategies should strive for an integrated management program with minimal number of applications of the chemical without sacrificing control.

Overall, WCC-60 strongly endorses the EPA's consideration of pesticide resistance management as a basis for granting Section 18 emergency exemption registrations. As cancellations of pesticides as a result of FQPA concerns continue, many pesticides that provided rotational chemistries for insect, weed and disease control in crops, especially fruit and vegetable crops, have been and will be lost. That places phenomenal selection pressure on new pesticides, many of which have highly specific modes of action. For the control of key pests, these new pesticides (often reduced-risk pesticides) will be used widely, repeatedly, and almost exclusively in many instances. Maintaining their value by allowing the use of rotational chemistries as soon as possible under Section 18 exemptions is not only a sound concept but a very necessary one if these reduced-risk products are to have a long and valuable period of use.

Submitted on behalf of WCC-60 by Margaret Tuttle McGrath, Cornell University